MAJOR PARADIGM SHIFT IN EARLY 1990S IN UNDERSTANDING RENAL CANCER

A CLASSIFICATION …BASED ON UNDERSTANDING THE GENETIC ABNORMALITIES INVOLVED WILL BE ROBUST IN TERMS OF BIOLOGY, CLINICAL BEHAVIOUR AND RESPONSE TO THERAPY
GENETIC ALTERATION IN RCC CORRELATES STRONGLY WITH MORPHOLOGY

<table>
<thead>
<tr>
<th>HISTOPATHOLOGY</th>
<th>3p LOSS</th>
<th>VHL MUTATION</th>
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<tbody>
<tr>
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<td>Y</td>
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|             |         |             |
| CLEAR CELL  | 25      | 8           |
|            | 18      | 25          |

| PAPILLARY   | 1       | 7           |
|            | 0       | 8           |

| ONCOCYTOMA  | 2       | 3           |
|            | 0       | 5           |

| CHROMOPHobe | 0       | 3           |
|            | 0       | 3           |

FOSTER ET AL 1994 Somatic mutations of the von Hippel - Lindau disease tumour suppressor gene in non-familial clear cell renal carcinoma
The Pathology and Genetics of Renal Tumours
WHO v4

- Clear cell renal cell carcinoma VHL and 3p-
- Multilocular cystic renal neoplasm of low malignant potential
- Hereditary leiomyomatosis with RCC associated renal cell carcinoma Fumarate hydratase
- Papillary renal cell carcinoma c-met and chr 7+; Fumarate hydratase*
- Chromophobe renal cell carcinoma Multiple chromosome loss
  - Hybrid oncocytic chromophobe tumour Folliculin
- Collecting duct carcinoma
- Renal medullary carcinoma IN1 and sickle cell
- MiT family translocation renal cell carcinoma
  - Xp11 translocation renal cell carcinoma
  - t(6;11) renal cell carcinoma
- Mucinous tubular and spindle cell carcinoma Multiple chromosomal losses
- Tubulocystic renal cell carcinoma Fumarate hydratase*
- Acquired cystic disease associated renal cell carcinoma
- Clear cell papillary (tubulopapillary) renal cell carcinoma
- Succinate dehydrogenase deficient RCC SDHB, SDHC, SDHD
- Renal cell carcinoma, unclassified
- Papillary adenoma
- Oncocytoma
EPIDEMIOLOGY

- 350,000 cases worldwide in 2012
  - 10,000 pa in UK
- Rate doubling in 20 years
- Associated with
  - Obesity
  - Cigarette smoking
  - Hypertension
- 2-4% familial
Multilocular cystic renal neoplasm of low malignant potential

Multilocular cysts, lined by a single layer of cells with evident clear cell morphology
No solid areas of clear cell carcinoma
PAPILLARY RCC

- TYPE 1, TYPE 2, MIXED
- NUCLEAR GRADE (ISUP)

NEW DEFINITION FOR PAPILLARY ADENOMA

UNENCAPSULATED AND <15mm
RENAL CANCER AND MITOCHONDRIA 2013

• THERE IS NOW EVIDENCE THAT MUTATIONS IN THE MITOCHONDRIAL SDH AND FH GENES PREDISPOSE TO DIFFERENT TYPES OF RENAL CANCER

• FIFTEEN YEARS AGO NO-ONE WOULD HAVE SUSPECTED THIS
Hereditary leiomyomatosis and renal cell carcinoma (HLRCC)-associated renal cell carcinoma and fumarate hydratase

- FIRST REPORT TYPE 2 PAPILLARY
- SECOND REPORT LOW GRADE CDC (TUBULOCYSTIC)
- SUBSEQUENT REPORTS ARCHITECTURE MAY BE TUBULAR, PAPILLARY, TUBULOCYSTIC OR MIXED
- USUALLY SOLITARY TUMOUR
- NUCLEOLAR MORPHOLOGY
- MUTATION MUST BE DEMONSTRATED
Hereditary leiomyomatosis and renal cell carcinoma (HLRCC)-associated renal cell carcinoma and fumarate hydratase

- TYPE 2 PAPILLARY, TUBULAR OR TUBULOCYSTIC NEOPLASM
- NUCLEOLAR MORPHOLOGY
- FAMILY HISTORY
- YOUNG PATIENT
- AGGRESSIVE TUMOUR BEHAVIOUR
Succinate dehydrogenase–deficient renal carcinoma

• RCC
  – OFTEN <30 YRS
  – POSSIBLE FEMALE PREPONDERANCE
  – MALIGNANT POTENTIAL
  – CHARACTERISTIC MORPHOLOGY
  – SDHB IMMUNOCYTOCHEMISTRY
  – HEAD AND NECK PARAGANGLIOMA
  – PHAEOCHROMOCYTOMA
  – DEMONSTRATE MUTATION IN GERMLINE AND SOMATIC LOSS
Succinate dehydrogenase–deficient renal carcinoma

A: DNA from blood
B: DNA from tumour
CHROMOPHOBE CARCINOMA

CK7
CHROMOPHOBEBE CARCINOMA

• GOOD PROGNOSIS
  – >90% 5 YEAR SURVIVAL
• ISUP GRADE NOT APPLICABLE
• CAREFULLY NOTE
  – SARCOMATOID MORPHOLOGY
  – NECROSIS
  – EXTENSION BEYOND KIDNEY
COLLECTING DUCT CARCINOMA

- Medullary involvement
- Predominant tubular morphology
- Desmoplastic stromal reaction
- Cytologically high grade
- Infiltrative growth pattern
- Absence of other RCC subtypes or urothelial carcinoma
MiT family translocation renal cell carcinomas

- YOUNGER PATIENTS
- MIXED CLEAR CELL AND PAPILLARY
- VOLUMINOUS CYTOPLASM
- PSAMMOMA BODIES
- TFE3, more rarely B or C in nucleus
- CATHEPSIN K

**Xp11 TRANSLOCATIONS**
- tX;11, tX;17
- T6;11 – TFE B
MUCINOUS TUBULAR AND SPINDLE CELL RENAL CARCINOMA

TUBULAR COMPONENT

SPINDLE CELL COMPONENT
TUBULOCYSTIC CARCINOMA OF KIDNEY

WELL CIRCUMSCRIBED
TUBULAR OR MICROCYSTIC
SINGLE LAYERED CUBOIDAL EPITHELIUM
MILD NUCLEAR PLEOMORPHISM
MAY HAVE PROMINENT NUCLEOLI
LOW METASTATIC POTENTIAL ~10%
Acquired cystic disease–associated renal cell carcinoma

• 30 YEAR HISTORY OF RCC IN ESRD
• PREVIOUSLY CONSIDERED TO BE MOSTLY PAPILLARY
• NOW AT LEAST TWO NEW TYPES OF RCC RECOGNISED IN THIS CLINICOPATHOLOGICAL CONTEXT
  – ACKD ASSOCIATED RCC
  – CLEAR CELL PAPILLARY RCC IN ESRD
• 60% OF RCC IN ESRD
Acquired cystic disease–associated renal cell carcinoma

- Often encapsulated
- Often arising from cyst
- Solid tubulo-acinar more often than papillary architecture
- Fine luminal spaces
- Calcification & psammoma bodies
- Large cell with eosinophilic cytoplasm
- Only occasionally clear cell

SULE et al 2005
CLEAR CELL PAPILLARY RCC

- ACKD OR NON-CYSTIC ESRD
- TUBULO-PAPILLARY ARCHITECTURE
- MAY BE CYSTIC
- CLEAR CELL CYTOLOGY
- SUBNUCLEAR CLEAR CYTOPLASM
  - MIMICKING SECRETORY ENDOMETRIUM
- NO VHL MUTATION NOR 3P LOSS
- NO TRISOMIES OF 7 AND 17
- POSITIVE CK7, HIF1a, CA IX (cup like pattern)
- NEGATIVE CD10, AMACR, TFE3
METANEPHRIC ADENOMA

- MAY PRESENT DIAGNOSTIC DIFFICULTY WITH PAPILLARY RCC
- USUALLY INCIDENTAL BUT CAN BE LARGE
- UNIFORM WHITE-GREY-TAN LESION
- HIGHLY CELLULAR
  - COMPOSED OF TIGHTLY PACKED SMALL ACINI
  - SMALL CELLS WITH BASOPHILIC NUCLEI LACKING PLEOMORPHISM
  - BRANCHING ANGULATED TUBULES COMMON
  - SOME FOCI OF PAPILLARY ARCHITECTURE
  - PSAMMOMA BODIES
METANEPHRIC ADENOMA
METANEPHRIC ADENOMA V PAPILLARY RCC

- CK7 FOCAL, MINOR
- WT1 70% +
- CD57 90% +
- AMACR 10-12% +

- CK7 >80% (TYPE 1 >2)
- WT1 12% +
- CD57 5% +
- AMACR 90% +

CK7 AND AMACR FAVOUR PRCC WHILE CD57 FAVOURS MA

FISH
MA Usually normal copy number chr 7, 17
PRCC chr 7+ and 17+ in majority

90% OF MA HAVE THE BRAF V600E MUTATION
Unclassified renal cell carcinoma

- USUALLY HIGH GRADE OFTEN WITH SARCOMATOID OR RHABDOID MORPHOLOGY
- MAY ON OCCASION BE A LOW GRADE TUMOUR WITH NO RESEMBLANCE TO DEFINED ENTITIES
- AS A GROUP THESE HAVE A POOR PROGNOSIS
- GENETIC INVESTIGATIONS MAY HELP WITH CLASSIFICATION eg VHL MUTATION AND 3p-
EMERGING ENTITIES

• ALK ASSOCIATED RCC
  – May be associated with sickle cell trait
  – Some indicative morphological features
  – ALK1 positive immunocytochemistry
  – t2:?? Translocation
    • Vin; EML4; TPM3; Copy number

• RCC WITH MONOSOMY 8
  – TCEB1 mutation and loss
  – Thick fibromuscular bands,
  – Clear cell cytology with voluminous cytoplasm
  – Clear cell renal cell carcinoma-like acinar areas tubular and focally papillary architecture

• THYROID FOLLICLE LIKE RCC
  – Characteristic thyroid like morphology
  – TTF-1 and thyroglobulin negative